

# Applications and Implications of Gold Therapy

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*Recent advances in biological, chemical and medical disciplines are now providing a better understanding of the processes whereby the complexes of gold exercise their physiological and pharmacological effects. As a result, exciting new developments in their therapeutic applications are occurring and others appear likely in the future.*

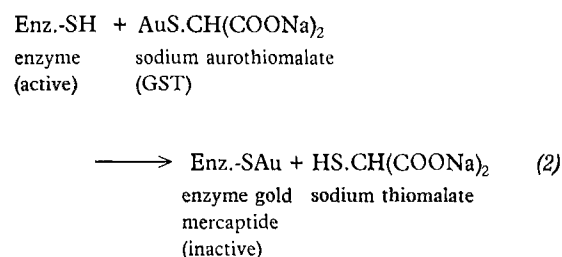
The unique therapeutic effects of gold compounds can be related to their chemical properties. As one of the group IB transition metals, gold forms a large number of coordination complexes. In monovalent or aurous form which is the valence form in all the therapeutically active gold compounds in current use, gold coordinates *inter alia* with sulphur- and phosphorus-containing ligands. In the case of the widely used drug disodium aurothiomalate (GST), the gold is coordinated with the sulphur in the thiomalate ion. In some recently developed drugs, however, the gold is coordinated or bonded to both sulphur and phosphorus. This is the case in AURANOFIN (AF) which is 2,3,4,6-tetra-O-acetyl-1-thio- $\beta$ -D-glucopyranosato-S-triethylphosphinegold(I). Compounds of gold such as GST and AF, like certain anti-tumor platinum compounds such as cis-diammine-dichloroplatinum(II) or CDDP, appear to owe their therapeutic potential not only to the ease with which they are transported in the body, but also to the occurrence of ligand exchange reactions, which result in a blocking or re-direction of biochemical reactions associated with certain diseases (1)

Such ligand exchange reactions can occur for example with the amino acid cysteine which is a unit in the

structures of a variety of enzymes and other proteins exercising important biological functions (Table I). In its exchange reactions with aurous complexes it is the reactive sulphydryl group (SH) of cysteine which is involved. The cysteine is converted to its gold mercaptide thus:



Enzymes which have cysteine units in their structures undergo similar reactions:



As a result of its conversion to its gold mercaptide the enzyme loses its catalytic activity, and biological reactions dependent upon this activity are inhibited or blocked.

Table I  
Aurous Derivatives of Crystalline Proteins and Enzymes. In part after (20) and (23)

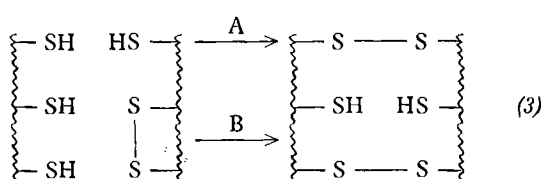
Gold labelling agent	Protein or enzyme	Molecular weight	Gold binding sites
$\text{Au(CN)}_2^-$	flavodoxin	15 000	cys 128 (cys 53)
	carbonic anhydrase	30 000	his 128/H <sub>2</sub> O
	liver alcohol dehydrogenase	80 000	cys 240 (adenine hydrophobic pocket)
$\text{AuI}_4^-$	Bence-Jones protein (part of an immunoglobulin)	12 500	?
	myoglobin	17 000	close to the haem group
	chymotrypsin	25 300	?
$\text{AuSNa}_2\text{C}_4\text{H}_3\text{O}_4$ (gold sodium thiomalate)	$\beta$ glucuronidase	—	probably SH reactive sites
	cathepsin-D	—	probably SH reactive sites
	succinic dehydrogenase	—	probably SH reactive sites

**Table II**  
**Comparison of the Effects of Sulphydryl-Blocking Agents on Lysosomal Enzyme Activity**

Inhibitor	Enzyme inhibition, per cent Inhibitor/sulphydryl molar ratio					
	0.01	0.05	0.1	1.0	10	25
N-Ethylmaleimide (NEM)	—	—	10	25	28	—
p-Chloromercuribenzenesulfonic acid (pCMBS)	7	9	10	25	42	—
Gold sodium thiomalate	12	20	25	27	30	—
Silver nitrate	—	—	31	40	51	—
Gold chloride	—	—	30	41	55	—
Iodoacetamide	—	—	—	—	—	38

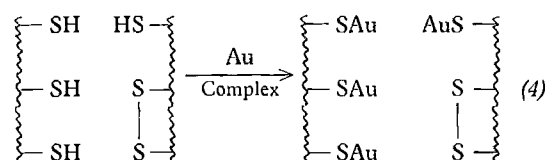
Certain detrimental reactions performed by enzymes and which will be described below, appear to contribute to or result in pathobiological processes of connective tissue disorders such as rheumatoid arthritis. Inflammation and misdirected immunological activity (auto-immunity) are the hallmark of these disorders. The underlying pathobiology is characterized to a major extent by lysosomal enzyme action detrimental to the articular structures. Such action can, however, be inhibited by complexes of gold or other sulphydryl-blocking agents (Table II).

A possible contributing factor to connective tissue disorders such as rheumatoid arthritis is the depletion of protein sulphydryl groups (2 to 5) arising from an apparent failure of metabolic redox mechanisms to reverse tissue sulphydryl oxidation. This effect is accentuated by the inflammatory process of superoxide formation. Protein sulphydryl oxidation can result in protein disulphide interchanges and ensuing alterations in native protein structure:



where A is the tissue SH oxidation brought about by oxygen or superoxide and B the intermolecular SH-disulphide interchange.

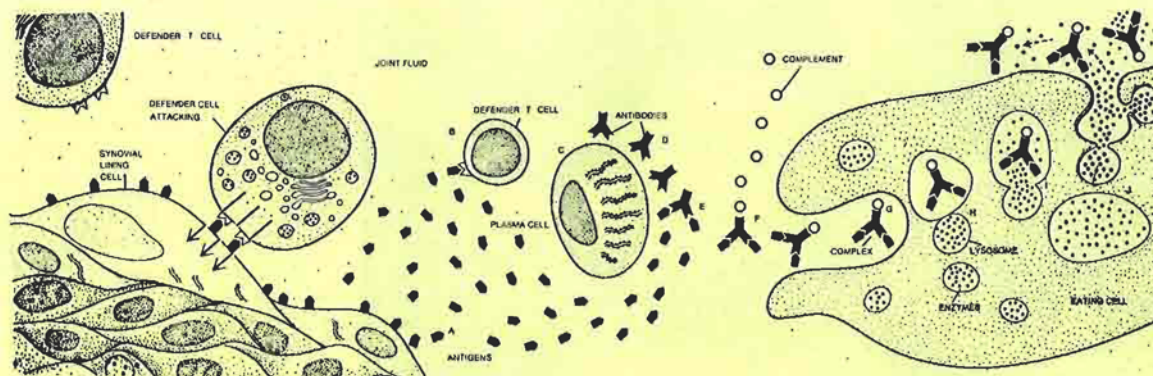
Such changes in conformational (autologous) protein structure are likely to elicit destructive immunological responses directed against the altered protein. Blockage of protein sulphydryl groups by gold as in the equation:



and avoidance by this means of the sulphydryl oxidation and disulphide interchange reactions (6) illustrated in equation (3) should prevent such deleterious effects as those which result, for example, from the denaturation of human gammaglobulin. This latter reaction has been shown to occur in the inflamed joints of rheumatoid subjects, apparently as a result of lysosomal enzyme action. Articular damage is perpetuated by alteration of gammaglobulin and other tissue components and this elicits an immune response, such as the formation of an antibody called rheumatoid factor (autoantibody) directed against

**Table III**  
**Major Cells of the Immune System and their Functions**

Cell type	Function
<b>T Lymphocyte</b>	cellular immunity directed against tissue grafts (transplants), tumors, viral, fungal and protozoal immunity
Helper cell	modulates and controls the immune response
Suppressor cell	modulates and controls the immune response
Memory cell	retains capacity to respond to future antigenic challenges
Killer cell	rejects grafts, tumors and 'non-self' cells
<b>B Lymphocyte</b>	forms antibodies, primarily providing bacterial and viral immunity
Plasma cells	
<b>Monocyte/macrophage</b>	processes antigens to stimulate immune response and interacts with lymphocytes



**Fig. 1** Schematic representation of events resulting from an autoaggressive disease initiated and perpetuated by the immune system (autoimmune disease). The surface of the synovial lining cells is altered by the presence of antigens (A), which causes the defender cells (lymphocytes and monocytes) to be confused and attack. The antigens (A) are also released into the joint fluid where they stimulate other cells (B) and the production of antibodies (C and D). Antibodies attached to antigens (E) attract and join with complement (F). The triple complexes thus formed are phagocytized (swallowed) by eating cells (G) and brought into contact with lysosomes (H and I) by which they would normally be digested. In the rheumatoid disease process, however, these powerful enzymes are released into the surrounding joint fluid where they damage joint tissue

altered gammaglobulin. Alteration or denaturation of human gammaglobulin can be prevented by the action of sulphhydryl-reactive agents such as gold, histidine and penicillamine (6).

### Altered Immune Functions and Induction of Human Auto-immune Disorders

Alterations in the structures of native proteins trigger immune responses. In rheumatoid arthritis, these responses ultimately take the form of tissue injury promoted by lysosomal enzymes (Figure 1). The inaugural event may be a viral infection of the connective tissues that sets into motion destructive immuno-pathological processes in which a varied population of lymphocytes plays a central role.

One must appreciate that the immune system is responsible for distinguishing one's own tissues and cells as 'self' from tumor cells or foreign invading particles (bacteria, viruses, fungi, etc.). This is a vitally important task and involves many complicated interactions. For the sake of brevity, two basic immune responses are considered in relation to the pathogenesis of rheumatoid arthritis: one that results in the production of antibodies and one in which white blood cells, usually lymphocytes and monocytes, react directly with foreign substances or tumor cells (antigens) to destroy them. This latter response has only recently been studied and has been found to be highly complex because several populations of lymphocytes are involved. These include, for example, B and T cells (Figure 2), each with their particular effector function (Table III). Moreover, these lymphocyte populations may be further classified into sub-populations of memory, killer,

helper and suppressor cells, with finely tuned functions for the immune response. The wide variations in reactivity of lymphocytes are thought to be genetically conferred and can be traced to a diverse spectrum of receptors for antigens found on the surfaces of these cells. These surface receptors trigger and control the cellular processes of tolerance to 'self', antibody production and cellular immunity, which appear to be susceptible to modification by coordinated heavy metal complexes.

Therapeutic *in vivo* as well as *in vitro* studies indicate that gold binds to lymphocyte membranes and accumulates within lymphocyte cells. The notion that binding of gold to lymphocytes also affects the latter's function is supported by the profound changes observed during chrysotherapy.

### The Effect of Gold on Cellular Biological Functions

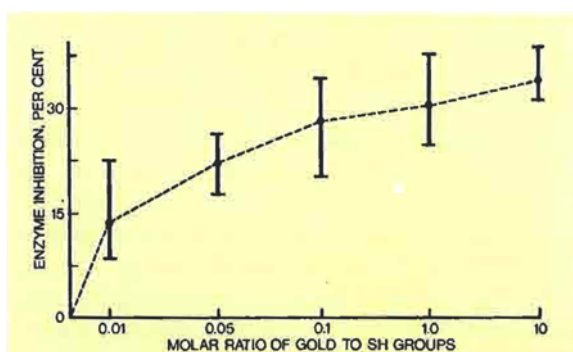
Excessive homeostatic protective mechanisms, for instance in the febrile response and enlargement of lymph glands during a throat infection, can result in such swelling and tissue inflammation as to cause greater injury than the inaugural infection. In rheumatoid arthritis such over-reaction, in the form of joint inflammation, perpetuates the disease process by contributing to tissue injury that brings into play previously described immune (autodestructive) processes performed by lymphocytes directed against altered or injured tissue sites (Figure 1). The therapeutic action of gold and other sulphhydryl-reactive agents could thus be either through the inhibition of enzyme activity or through the prevention of protein disulphide interchange. If injury by





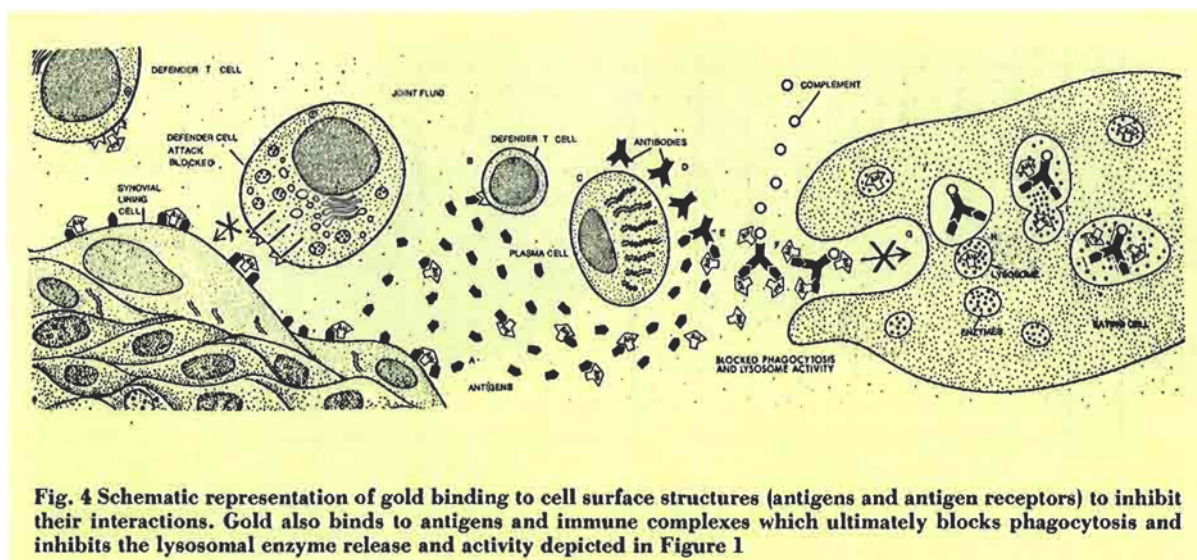
**Fig. 2** Scanning electron micrograph of 'defender' white cells involved in the defence of the body against disease. The 'hairy' cells are B lymphocytes, derived from bone marrow and responsible for the production of antibodies. The 'smooth' cells are T lymphocytes, another type of defender cell, processed in the thymus and involved in the recognition of foreign substances  
x 5 000

lysosomal enzyme and changes in original protein structure are not prevented, these deleterious events are likely to contribute to inflammation and to the immunological reactions described above. The authors have indeed observed that the hydrolytic and proteolytic action of the lysosomal enzymes beta-glucuronidase and cathepsin-D are inhibited by gold compounds at pharmacologically achievable concentrations when these are added to synovial (joint) fluid or synovial tissue taken from rheumatoid subjects and propagated in culture (Table II and Figure 3). Inhibition by gold of lysosomal enzyme activity would thus prevent autodigestive injury to the articular structures such as cartilage, tendon and bone. Phagocytosis of immune complexes, a prelude to lysosomal injury, is also inhibited by gold at pharmacologically achievable levels (Figure 4) (7).



**Fig. 3** This graph of the inhibition of acid hydrolase activity *vs.* the molar ratio of gold to sulphhydryl groups in synovial fluid illustrates the action of gold sodium thiomalate on enzymic activity

Similarly, immunological injury to the connective tissues by lymphocytes responding to altered or denatured protein can also be decreased by suppressing lymphocyte function. Hence, suppression of a B cell effector function would cause a decline in the production of autoantibodies such as rheumatoid factor and immunoglobulins (Table IV), while suppression of T lymphocytes would lessen cellular cytotoxic destructive processes. Indeed, we have observed, under therapeutic conditions simulated *in vitro*, that the following lymphocyte metabolic processes are inhibited by gold: respiration; RNA, DNA and protein synthesis and proliferation or cloning. A unifying hypothesis for these observations is that gold compounds suppress hypermetabolic functions associated with excessive phagocytic and lymphocytic activity. This effect on cellular functions is reflected in the suppression of rapid mitochondrial respiration. We have observed the inhibition of succinic acid dehydrogenase and other respiratory chain enzymes when mitochondrial preparations obtained from rats with induced arthritis are incubated with gold compounds at pharmacological concentrations. Leninger (8) has reported that suppression of mitochondrial respiration correlates with blocking of mitochondrial protein sulphhydryl groups following incubation with heavy metal complexes. Thus, suppression of cellular metabolic functions by coordinated metal complexes suggests new therapeutic applications including the treatment of disorders associated with excessive cell proliferation. Notable examples are cancerous disorders, including those of the immune system exemplified by lymphoproliferative disorders as in lymphomas, sarcomas, leukemias, etc.



**Fig. 4** Schematic representation of gold binding to cell surface structures (antigens and antigen receptors) to inhibit their interactions. Gold also binds to antigens and immune complexes which ultimately blocks phagocytosis and inhibits the lysosomal enzyme release and activity depicted in Figure 1

### Applied Gold Therapy

Some of the current theories and observations pertaining to the pathobiology of rheumatoid arthritis and related disorders have been reviewed briefly. The misdirected or aberrant immunological response is, no doubt, a major contributor to the inflammation and damage sustained by the joints and the connective tissues. The final expression of this injury, as we have indicated, results from a complicated series of biochemical events that can be partially or totally inhibited by complexes of heavy metals such as gold (see equation (1) and Figure 4).

The goal of therapy is to inhibit or reverse the pathobiological events that result in tissue injury and inflammation. If based on gold, such therapy may be double-edged because it can also inhibit essential biochemical processes and thereby cause serious and even lethal adverse reactions. Hence, as is often the case with drug therapy, a difficult course has to be followed in order to achieve success.

### Historical Aspects of Chrysotherapy

Gold was used for therapeutic applications by the ancient Egyptian and Chinese civilizations and possibly even earlier. It is doubtful, however, whether the elemental gold then used was at all active or effective. In contrast, the solutions prepared by alchemists by dissolution of gold in aqua regia were so active and highly toxic that their use was normally by topical application in the treatment of disorders such as leprosy.

With the discovery by Pasteur in the late 19th century of micro-organisms and of their causative role in infectious human diseases, chemotherapy evolved as the art of using an agent that would selectively inhibit or destroy infectious organisms without at the same

time harming their human hosts. Gold cyanide was observed by Dr. Robert Koch to inhibit the growth of tubercle bacilli, while success with other metal derivatives (Ehrlich's magic bullets) was reported in the treatment of syphilis. These observations encouraged a search for 'gold bullets' for the treatment of rheumatoid arthritis which was initially also thought to be caused by infection with the streptococcus.

It is probably the fortuitous use of gold complexes by Landé and the improvement of articular manifestations in patients with tuberculosis and coincident rheumatoid arthritis that led Forestier in 1929 to use such complexes specifically for the treatment of rheumatoid arthritis (9). He was able to confirm the benefits of gold therapy, but serious toxic and sometimes fatal reactions were associated with administration of the gold complexes which he studied and the resulting apprehension understandably limited their use. Subsequently, the use of gold-sulphur complexes was found to be safer though concern regarding their toxicity influenced their dosage and the frequency of their administration. The latter were empirical and the aim was to avoid toxicity while at the same time retaining efficacy. It is not surprising that confusion regarding the efficacy of gold compounds for the treatment of rheumatoid arthritis persisted until the late 1950's when a carefully conducted multi-centre study controlled by the Empire Rheumatism Council established that gold was an effective agent with remittive potential (10). Even after this detailed study, dosage was limited to one 50 mg injection per week for a 20-week period and then usually discontinued for fear of cumulative toxicity. At that time the custom was not to exceed an accumulated dosage of 1 g of GST, though due to the



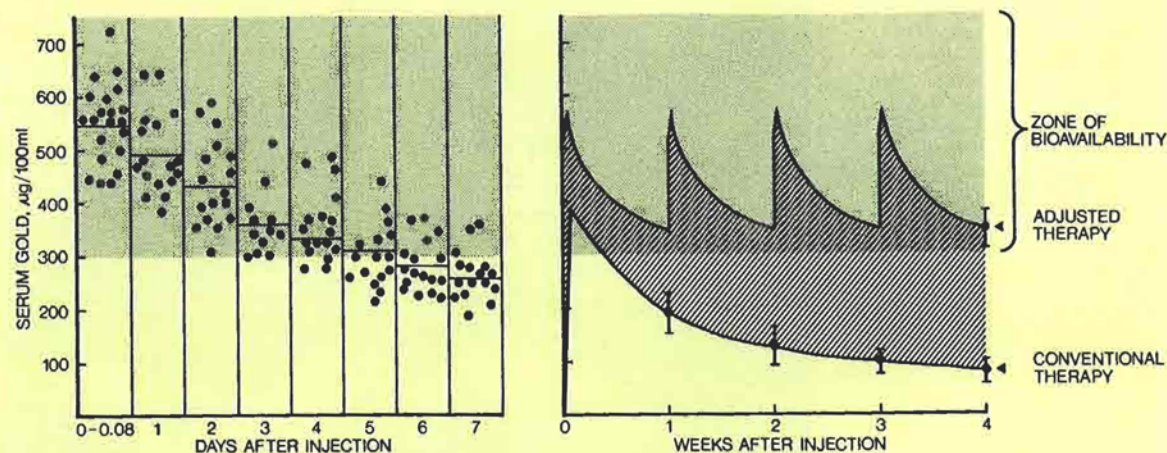


Fig. 5 Hourly and daily blood serum gold (as Au) values following the administration of 50 mg gold sodium thiomalate to patients at the 20th week of treatment (left) and schematic pattern of blood gold availability during the ensuing 4 weeks (right). With conventional therapy, administration of gold is discontinued after the 20th injection and blood serum gold values fall below the zone of bioavailability within days. With individualized or adjusted therapy, the treatment is maintained and weekly administration of gold, which is monitored by blood gold determinations, facilitates bioavailability

high relapse rate of disease it was later decided on an empirical basis to continue 'maintenance therapy' with 50 mg of GST administered monthly. With increasing knowledge of modern pharmacokinetics and wider experience, gold therapy has become safer and more effective in the treatment of rheumatoid arthritis. Recently, moreover, other serious medical disorders that seem to share common disturbances of immune function, resulting in injury to the connective tissues including articular structures as described earlier, have also been treated with gold compounds. To date, however, gold therapy is still largely administered on an empirical rather than individualized regimen.

#### Gold Administration — Blood Level Response

The development of atomic absorption spectrophotometry has made possible rapid and accurate analysis for gold in blood and other tissues (11). Information gained from blood gold analysis by this technique has been applied by the authors in an attempt to improve the current empirically based mode of gold administration. The effects of dosage, frequency and duration of gold administration were studied and relationships between blood gold concentrations and distribution of gold to plasma proteins, cellular blood components and other tissues were observed. After noting correlations between blood gold (as Au) levels and clinical response, adverse reactions and changes in specific laboratory parameters including the effects on immune function, this information was consolidated in the formulation of a therapy schedule (12). Gold administration monitored by blood gold level could then be in-

dividualized, adjusted and continued weekly to maintain a specified range of gold (as Au) concentration in the blood (300 to 700 µg/dl).

#### Variations in Patients' Blood Gold Levels

The serum gold concentration and subsequent decay patterns following a 50 mg injection of GST are shown in Figure 5. Moderate individual variations in both peak levels and subsequent daily values are not uncommon. Thus, patients 'sensitive' to gold, who constitute approximately 10 per cent of the total, respond with rather high serum gold levels; a pattern that usually persists throughout the course of therapy. Conversely, in another 10 per cent of the patients, after the same 50 mg intramuscular dose of GST, blood gold levels above 300 µg/dl are often not sustained. These patients require, and receive, larger doses to maintain blood gold levels in the indicated range of 'bioavailability'. We postulate that differences observed in serum gold response may be due to differing rates of distribution, retention and excretion of gold. These rates are possibly affected by variations in gold ligands, such as cysteine and histidine, to which the GST is exposed after it has been administered.

#### Therapeutic Response

Through experience gained in monitoring blood gold levels, it was established that gold administration need not arbitrarily be curtailed after 20 weekly injections, as is customary with the empirical regimen if a beneficial response is not achieved. Conversely, when a successful response is achieved, individualized administration can avoid the high relapse rate and

**Table IV**  
**Changes in Laboratory Parameters in Patients Receiving Individualized Gold Sodium Thiomalate (GST) Chrysotherapy**

Parameter	Normal range	Years of therapy				
		admission	1	2	3	4
Number of subjects		39	39	23	16	10
IgA, mg/dl	50 to 400	325±39(a)	213±21(c)	249±42(c)	233±54(d)	251±109
IgG, mg/dl	600 to 2000	1494±75	1228±71(d)	1229±132(e)	1134±134(d)	1002±88(d)
IgM, mg/dl	20 to 200	130±16	77±8(c)	65±8(c)	61±9(d)	63±13(e)
Rheumatoid factor titer (reciprocal tube dilutions)		8.6±0.3	4.6±0.6(c)	3.8±0.8(c)	3.4±1.0(d)	3.0±1.5(e)
(Erythrocyte sedimentation rate ESR, Wintrobe), mm/hour	20	37.7±2.1(b)	25.1±2.0(c)	24.3±2.6(c)	28.6±3.6(e)	32.1±6.0
Leukocytes/mm <sup>3</sup>	4100 to 10900	7752±275(b)	6859±279(c)	6281±292(c)	6753±439(d)	6836±706
Lymphocytes/mm <sup>3</sup>	820 to 2180	1921±93(b)	1618±101	1583±93(c)	1449±76(c)	1419±192(e)
Cumulative dose GST, mg						
Mean		0*	2106	3993	5309	8747
Range		0*	1065 to 2885	2635 to 5560	4760 to 7735	5385 to 15160

± Standard error of the mean (SEM)

\* The values reflect cumulative GST dosage administered in the course of this study

(a) 37 subjects

(b) 44 subjects

(c) P < 0.001

(d) P < 0.01 by paired variate 't' statistics

(e) P < 0.05

The change in values and/or decline in statistical significance after the second year resulted from loss of the best responders who achieved remission

disease exacerbation often encountered as the frequency of injections is curtailed with empirical dosing. An added advantage of weekly dosing on the basis of blood gold levels is that gold administration can be sustained in order to achieve a satisfactory clinical response, which may require 18 months or more (13,14). Concern regarding cumulative gold toxicity, if the 300 to 700 µg/dl range is not exceeded, has largely been dispelled by comprehensive laboratory assessments that were made while weekly gold therapy was continued for more than 5 years. Cumulative doses in excess of 15 g GST have been administered without evidence of cumulative toxicity or adverse reactions. So far, the dreaded problem of bone marrow toxicity has not been encountered in more than 150 subjects who have received individualized chrysotherapy. (Thrombocytopenia has been observed with individualized therapy and is felt to be an idiosyncratic rather than a toxic reaction since bone marrow damage was not detected by microscopic examination). Incidence of gold dermatitis, which usually does not dictate termination of gold therapy, and incidence of renal injury, which does require termination of therapy, are approximately the same as with the empirical regimen. Based on blood gold levels and gold excretion, these adverse reactions appear to be manifestations of idiosyncrasy rather than toxicity.

The observations reported here have created in the medical literature some controversy regarding the

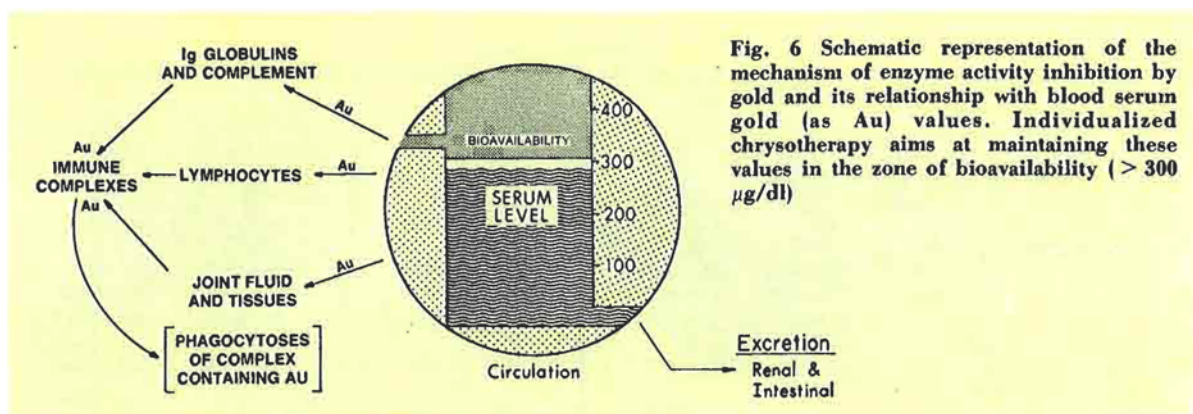
validity of individualized therapy and the significance of blood gold levels (15,16). Conflicting studies, however, utilized fixed rather than individualized dosage and this was not continued weekly for the extended treatment interval instituted by the authors of this article. According to the latter's experience, individualized chrysotherapy has yielded significantly greater clinical benefits and these have correlated with the suppression of several laboratory immunological parameters. Thus, the levels of lymphocyte counts, immunoglobulins and the rheumatoid factor which are thought to contribute to the pathogenesis of the disease have all declined (Table IV).

### Gold Kinetics — Delivery and Tissue Distribution

How is gold delivered to the target or effector sites active in the pathobiology of rheumatoid arthritis? Factors influencing gold distribution may include:

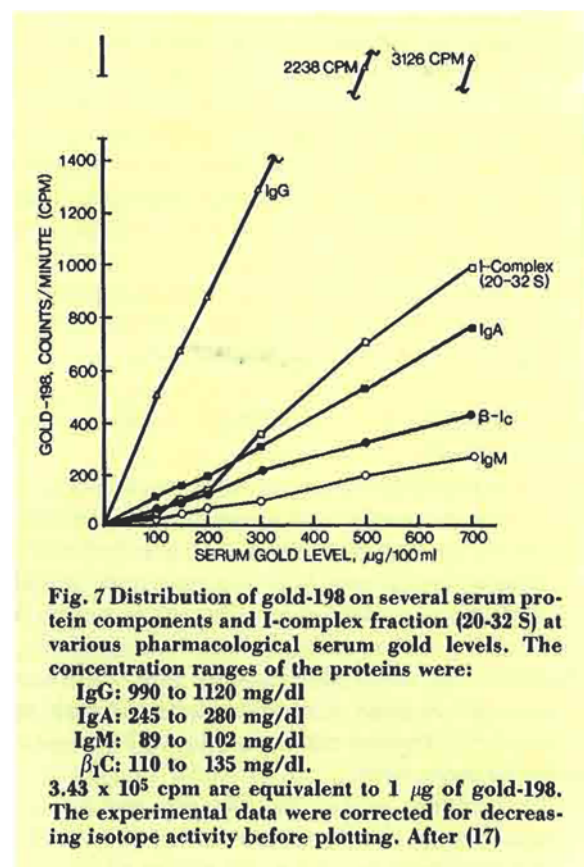
- (1) Mass action, for which the concentrations of gold complex in the blood and the extent to which these are sustained are important
- (2) The nature of the gold complex. For example, it may be hydrophobic or hydrophilic and ionic or non-ionic. Its properties may affect cellular membrane penetration
- (3) The stability of the gold complex, and in particular whether it remains intact or whether the organic ligands bonded to the gold are degraded.





Aurous complexes bind readily on a mass action basis to blood proteins, formed elements and other tissue components. Therefore, these compete for gold with effector sites. Moreover, gold-sulphur and gold-phosphorus compounds such as GST and AF have limited stability which would seem to dictate frequent administration to facilitate distribution of the active agent to potential effector sites (Figure 6). We postulate that the enhanced response achieved by continuing weekly administration may be related to the more frequent and higher peaks achieved in serum gold content (Figure 5). During these peaks, greater availability of the active agent would be predicted;

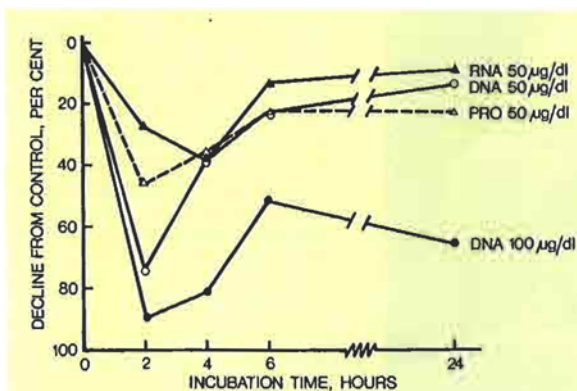
improved distribution in tissue would facilitate binding to reactants in the inflammatory and immune system at effector sites (Figure 4). Bioavailability in excess of 300  $\mu\text{g/dl}$  appears to be required for binding of gold to immune complexes and lymphocytes (Figure 7) (17). When these conditions for bioavailability of the gold are sustained through adequate dosing, parameters such as immunoglobulins, rheumatoid factor titer and lymphocyte counts appear to respond to dosages (Table IV). Similarly, other pathobiological mechanisms — the inhibition of acid hydrolases and the suppression of phagocytic activity — are dependent on the bioavailability of the reactive gold complex. Hence, we postulate that the availability of gold to tissues affected by the disease process, as for example its availability for binding to immune complexes and lymphocytes at serum gold levels greater than 300  $\mu\text{g/dl}$  (Figure 6), may be an important consideration. This concept is also supported by *in vitro* studies made by other investigators and by our observations that inhibition of lymphocyte, monocyte and phagocytic function was clearly dependent on the concentration of aurous gold in blood being above 300  $\mu\text{g/dl}$ .



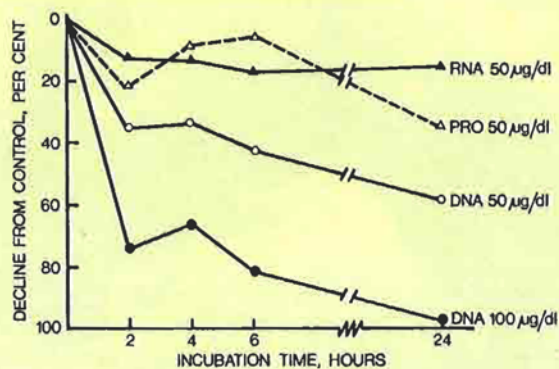
### Current Progress and Future Applications of Gold Therapy.

Gold compounds are currently considered to be amongst the more effective and remittive agents for the treatment of rheumatoid arthritis. Although therapeutic applications have largely been limited to this disorder, the use of gold-sulphur complexes has also been reported to be beneficial in the treatment of psoriatic arthritis and discoid lupus and more recently in the treatment of pemphigus vulgaris and bronchial asthma (18,19). Parameters of immune function, as the authors and others have recently reported, are clearly affected by chrysotherapy. Accordingly, wider application of gold therapy for those disorders involving 'autoimmune' response, especially excessive B cell function, can be anticipated. Indeed, these new frontiers may extend to the field of cancer therapy. It





**Fig. 8** Relative effects with time of AURANOFIN (AF) (50 to 100 µg/dl) on DNA, RNA and protein synthesis (PRO) in RAJI cells, as measured by  $^3\text{H}$ -thymidine,  $^3\text{H}$ -uridine and  $^3\text{H}$ -leucine uptake respectively. AF was added at time zero and the cells were labelled for only the last 2 hours of the exposure period. The decline of activity is relative to that in a control sample

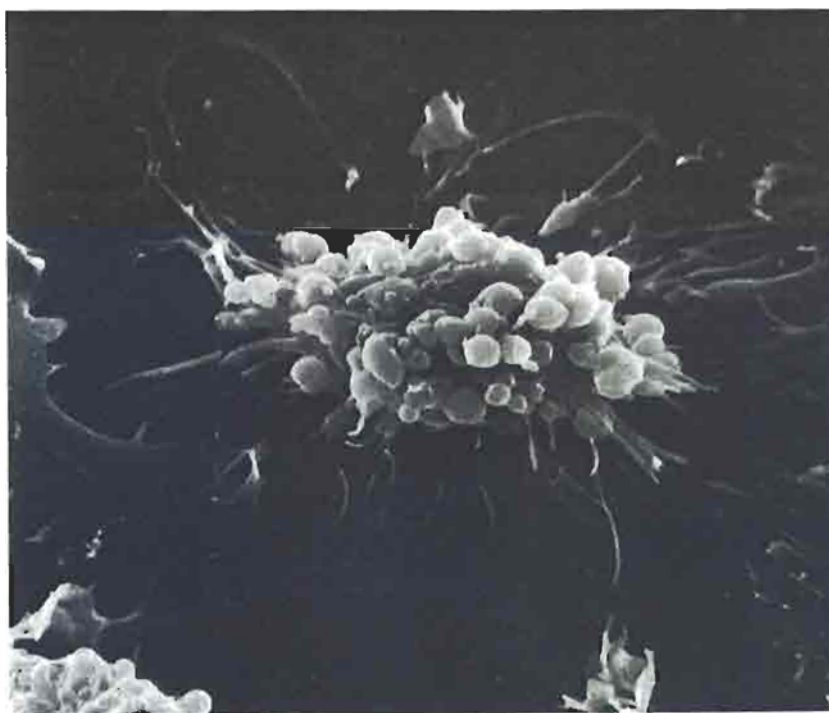


**Fig. 9** Relative effects with time of AURANOFIN (AF) (50 to 100 µg/dl) on DNA, RNA and protein synthesis (PRO) in HeLa cells, as measured by  $^3\text{H}$ -thymidine,  $^3\text{H}$ -uridine and  $^3\text{H}$ -leucine uptake respectively. AF was added at time zero and the cells were labelled for only the last 2 hours of the exposure period. The decline of activity is relative to that in a control sample

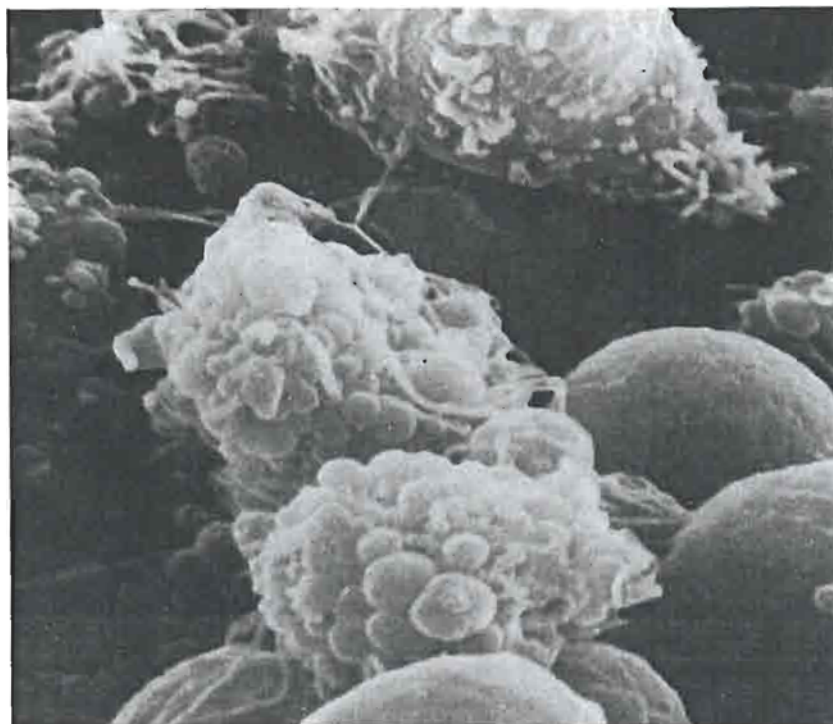
has, for example, been shown that certain tumors elicit an immune (B lymphocyte) response in which the antibody covers or blocks tumor determinants that would otherwise be attacked by killer or cytotoxic T lymphocytes (Table III). Hence, the suppression of a B cell function by gold compounds could prevent the formation of such blocking antibodies and thereby facilitate tumor destruction by the T cells.

During the past year, a new formulation in which gold is stabilized by both sulphur and phosphorus ligands (20) was introduced for the treatment of rheumatoid arthritis. To date, applied experience

indicates that this agent (AF) is effective in the treatment of rheumatoid arthritis and has several advantages over conventional gold-sulphur complexes. These advantages include oral administration and significantly lower incidence of serious adverse reactions. The hydrophobic and non-ionic characteristics of AF facilitate cell membrane penetration and as a result the compound affects cellular biochemical function at lower blood concentration. Hence, the serious adverse reactions which have been encountered in the use of gold-sulphur complexes available so far may be avoided.



**Fig. 10** The marked surface blebbing and rounding in this HeLa cell is the result of a 6-hour treatment with 75 µg/dl of AURANOFIN x 4 000



**Fig. 11** Blebbed peripheral lymphocytes such as these are observed in patients receiving AURANOFIN. They can usually be detected after 4 to 8 weeks of therapy and represent approximately 8 to 10 per cent of the population. Cellular blebbing is not observed in rheumatoid arthritis subjects prior to chrysotherapy x 5 500

In studies performed with proliferating lymphocyte and human cancer cells (African Burkitt's lymphoma and carcinoma of the cervix grown in the laboratory) the authors have also observed dramatic antiproliferative action by AF as reflected by the suppression of DNA, RNA and protein synthesis (21,22) (Figures 8 and 9). We have observed a gold dose-dependent surface morphological change illustrated by blebbing and pitting not only in cancer cells, but also in lymphocytes obtained from patients receiving AF therapy (Figures 10 and 11). These dramatic morphological changes appear to reflect effects of gold compounds additional to the suppression of immunological parameters described earlier. The antiproliferative effect of coordinated gold complexes

may be cell cycle-dependent, that is selectively directed toward rapidly proliferating or cloning lymphocytes involved in the autoimmune or autoaggressive disease process. It is also possible that the antiproliferative action of coordinated heavy metal complexes such as AF and CDDP exerts a regulatory or modulating effect on the immune response, perhaps through the antiproliferative effect exerted on specific cloning sub-populations of T lymphocytes (suppressor, helper, etc.).

The therapeutic potential of heavy metal complexes is therefore considerable and its further investigation should prove rewarding not only for the treatment of rheumatoid arthritis but also for that of a number of other diseases.

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